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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Announcement of Requirements and Registration for Up For A Challenge (U4C) – Stimulating Innovation in Breast Cancer Genetic Epidemiology

Authority: 15 U.S.C. 3719

AWARD APPROVING OFFICIAL: Douglas R. Lowy, Acting Director, National Cancer Institute

SUMMARY: The National Cancer Institute’s (NCI) Division of Cancer Control and Population Sciences (DCCPS) announces that they are partnering with Sage Bionetworks to launch “Up For A Challenge (U4C) – Stimulating Innovation in Breast Cancer Genetic Epidemiology” (the “Challenge”) to encourage unique approaches to more fully decipher the genomic basis of breast cancer. Utilizing innovative approaches, the goal of this Challenge is to identify new genes or combinations of genes, genetic variants, or sets of genomic features involved in breast cancer susceptibility. In addition, the NCI aims to advance innovation in the field of genetic epidemiology by making data more widely available, increasing the amount and diversity of minds approaching a difficult scientific

problem, and promoting broader collaborations. This Challenge is being launched under the America COMPETES Reauthorization Act of 2010.

DATES:

Challenge Opens: June 15, 2015

Challenge Entries: Due January 15, 2016 (8PM EST)

Challenge Judging: January 16, 2016-March 31, 2016

Winners Announced: April 16-20, 2016

The NCI will announce any changes to the timeline by amending this Federal Register notice. This Challenge will be supported by Sage Bionetworks (<https://www.synapse.org/upforachallenge>) on behalf of the NCI.

ADDRESSES: To register for this Challenge, Challenge participants may access the registration on the Challenge website (<https://www.synapse.org/upforachallenge>).

Access to this website may also be found by searching the www.challenge.gov site for “Up For A Challenge.”

FOR FURTHER INFORMATION CONTACT: Elizabeth M. Gillanders, Ph.D., NCI, (240) 276-6764; Leah E. Mechanic, Ph.D., NCI, (240) 276-6847 or NCIUpForAChallenge@mail.nih.gov.

SUPPLEMENTARY INFORMATION:

Subject of Challenge Competition

In order to stimulate innovation, the National Cancer Institute's (NCI) Division of Cancer Control and Population Sciences (DCCPS) is launching a prize competition to inspire novel cross-disciplinary approaches to more fully decipher the genomic basis of breast cancer, called "Up For A Challenge (U4C) – Stimulating Innovation in Breast Cancer Genetic Epidemiology" (the "Challenge") using the America Creating Opportunities to Meaningfully Promote Excellence in Technology, Education, and Science (COMPETES) Reauthorization Act of 2010.

The goal of this Challenge is to use innovative approaches to identify novel pathways—including new genes or combinations of genes, genetic variants, or sets of genomic features—involved in breast cancer susceptibility in order to generate new biological hypotheses.

To that end, several data sets have been gathered and will be made available for use in the Challenge; some of these will be released for the first time. In addition, Challenge participants will be free to use any other publicly available data sets (subject to compliance with applicable terms and conditions) for the purposes of developing and applying methods for identification of the novel pathways.

Breast cancer is the most commonly occurring cancer, and the second most common cause of cancer deaths in women in the United States. An estimated 231,840 new cases of invasive breast cancer are expected to be diagnosed among women (2,350 in men) in the U.S. during 2015 with an estimated 40,730 deaths. Despite advances in breast cancer therapies, breast cancer remains a major public health burden. One

approach to reduce overall occurrence and mortality from breast cancer is to develop ways of identifying women who are at increased risk for breast cancer.

Epidemiologic studies suggest that genetic factors play a key role in determining who is at increased risk of developing breast cancer, as well as what type of cancer they develop. To date, genome-wide association studies (GWAS) have helped researchers identify more than 90 common genetic variations. Although GWAS have greatly increased our understanding of the genetic components of breast cancer susceptibility, the results to date explain only a small proportion of the estimated genetic contribution to the risk of breast cancer. However, shifting the focus of analysis from individual genetic variants (also known as single nucleotide polymorphisms or SNPs) to pathways (i.e. combinations of genes, genetic variants, or sets of genomic features), could lead to the identification of novel gene sets involved in breast cancer risk.

This Challenge provides an opportunity to examine the heritable contribution to racial disparities, by facilitating access to GWAS data sets from African American, Asian, European, and Latino women. African American women are known to have a lower incidence of breast cancer, but survival is lower for African American than for non-Hispanic white women at every stage of diagnosis. Meanwhile, Asian women have the lowest rates of breast cancer incidence and mortality compared with non-Hispanic white, African American, and Hispanic/Latino women. Findings from this Challenge may provide insights into some of these observed differences.

As more fully described below, participants are invited to use innovative approaches to identify novel pathways—including new genes or combinations of genes, genetic variants, or sets of genomic features—involved in breast cancer susceptibility.

Besides developing a better understanding of cancer risk assessment, the identification of breast cancer susceptibility genes holds promise for providing therapeutic targets for drug development.

Statutory Authority

The NCI is authorized and established by Title IV, Part C, Subpart 1 of the Public Health Service Act, 42 U.S.C. § 285 to conduct and support research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients. Through this Challenge, the NCI aims to advance innovation in the field of genetic epidemiology by making breast cancer genetic epidemiology data more widely available, increasing the number and diversity of researchers addressing a difficult scientific problem, and promoting broader collaborations. Ideally, this would result in insights into the genetic epidemiology of breast cancer.

Official Rules:

Eligibility Rules for Participating in the Challenge and Winning

1. To be eligible to win a prize under this Challenge, an individual or entity—
 - a. Shall have registered to participate in the Challenge under the rules promulgated by the National Cancer Institute (as published in this notice);
 - b. Shall have complied with all the requirements under this section;
 - c. In the case of a private entity, shall be incorporated in and maintain a primary place of business in the United States, and in the case of an individual, whether participating singly or in a team, shall be a citizen or permanent resident of the

United States;

- d. May not be a Federal entity;
 - e. May not be a Federal employee acting within the scope of his or her employment and further, in the case of HHS employees may not work on their Entries during assigned duty hours. **Note:** Federal ethical conduct rules may restrict or prohibit Federal employees from engaging in certain outside activities, so any Federal employee not excluded under the prior paragraph seeking to participate in this Challenge outside the scope of employment should consult his/her agency's ethics official prior to developing an Entry;
 - f. May not be an employee of the NIH, a judge of the Challenge, or any other party involved with the design, production, execution, or distribution of the Challenge or the immediate family member of such a party (i.e., spouse, parent, step-parent, or step-child). Without limiting the generality of the foregoing, members of the Evaluation Panel which will score Entries and the NIH Judges, as well as their students are not eligible to participate in the Challenge.
- 2. Federal grantees may not use Federal funds to develop Challenge Entries unless consistent with the purpose of their grant award and specifically requested to do so due to the Challenge design, and as announced in the Federal Register.
 - 3. Federal contractors may not use Federal funds from a contract to develop Challenge Entries or to fund efforts in support of a Challenge Entry.
 - 4. An individual, Team, or entity that is currently on the Excluded Parties List (<https://www.epls.gov/>) will not be selected as a Finalist or prize winner.
 - 5. Whether singly or as part of a team or entity, each individual participating in the

Challenge must be 18 years of age or older.

6. An individual shall not be deemed ineligible to win because the individual used Federal facilities or consulted with Federal employees during the Challenge provided that such facilities and/or employees, as applicable, are made available on an equitable basis to all individuals and Teams participating in the Challenge.
7. Each individual (whether competing singly or in a team) or entity agrees to follow applicable local, State, and Federal laws and regulations.
8. Each individual (whether participating singly or in a team) and entity participating in this Challenge must comply with all terms and conditions of these rules, and participation in this Challenge constitutes each such participant's full and unconditional agreement to abide by these rules, which may also be found on the Challenge website (<https://www.synapse.org/upforachallenge>). Winning is contingent upon fulfilling all requirements herein.

All questions regarding the Challenge should be directed to Dr. Gillanders or Dr. Mechanic, identified above or by emailing NCIUpForAChallenge@mail.nih.gov and answers will be posted and updated as necessary at <https://www.synapse.org/upforachallenge> under Frequently Asked Questions.

Registration Process for Participants

To register for this Challenge, Challenge participants may access the registration on the Challenge website (<https://www.synapse.org/upforachallenge>). Access to this website may also be found by searching the www.challenge.gov site for "Up For A Challenge." Individuals may participate in the Challenge as individuals or as Teams. Details about participating as a Team are provided below:

1. After registration, you may participate alone or on a Team with other Challenge participants. To work on a Team, you may either create a new Team or join a pre-existing Team.
2. There is no maximum Team size.
3. All Teams must designate a Team Captain. Each individual member of a Team must be a registered participant in the Challenge.
4. Individuals may participate on multiple Teams, and Challenge Teams may merge (requiring mutual agreement of Team Captains). Individuals are allowed to leave a Team to work alone or join another Team.

Data Access Process

Once registered for the Challenge, participants must apply for controlled access to the designated Challenge genetic datasets following instructions on the Challenge website. Challenge participants may use any of these dbGaP datasets or any other datasets available to anyone (either publically available or available through controlled access) such as data from the Cancer Genome Atlas (TCGA) (<http://cancergenome.nih.gov/>) or the ENCyclopedia Of DNA Elements (ENCODE) project (<http://www.genome.gov/encode/>).

Data will be requested through database of Genotypes and Phenotypes (dbGaP) application process. Details regarding the process for requesting data are provided on the Challenge website (<https://www.synapse.org/upforachallenge>). Data Access Requests will be reviewed by the appropriate NIH Data Access Committees (DAC) to ensure that the proposed project is consistent with any Data Use Limitations for the requested dataset(s). NOTE: that any scientific collaborators, including contractors, who are not at

the same institution as the PI must submit their own DAR. Data cannot be shared with collaborators from other institutions until they have submitted an application (and explicitly named this collaborators) to use the dataset(s) from their institution(s) and have received approval. If Approved Users are provided access to NIH genomic datasets for inter-institutional collaborative research described in the research use statement of the DAR, and all members of the collaboration are also Approved Users through their home institution(s), data obtained through this DAR may be securely transmitted within the collaborative group.

Challenge participants who obtain data from dbGaP should note that they are agreeing to the NIH Genomic Data User Code of Conduct (http://gds.nih.gov/pdf/Genomic_Data_User_Code_of_Conduct.pdf) and they are agreeing to the terms of specific Data Use Certificates for each individual dataset requested (The model Data Use Certificate can be found here -- http://gds.nih.gov/pdf/Model_DUC.pdf). Note that individual datasets may have additional limitations in regards to use of the data. As the GWAS datasets obtained from dbGaP are considered controlled access data, individuals approved to use these data must abide by dbGaP security best practices in regards to the data

(http://www.ncbi.nlm.nih.gov/projects/gap/pdf/dbgap_2b_security_procedures.pdf).

If submitting a request to dbGaP for use of data for the Challenge, participants should be aware that the data requested should be used solely for the research purpose described in the Data Access Request, i.e. solely for the Challenge. New uses of these data outside this Challenge will require submission of a new Data Access Request.

Challenge Entries

As used in this notice, “Entry” is the information submitted in the manner and format specified on the Up For A Challenge (U4C) website

(<https://www.synapse.org/upforachallenge>). All Entries must be received by the applicable deadline. Entries submitted after a posted Challenge deadline will not be considered.

Entries may be submitted on behalf of a Team by any of its participants. It is up to each Team to organize its Entry(ies) and to follow the Challenge submission requirements. On submission of an Entry, Challenge participants must include the Team name under which they are submitting.

All final Entries must be submitted through the Challenge website on Synapse, following website instructions and should provide necessary and sufficient detail and annotation for reproduction of the submitted results. Information accompanying each Entry should include:

1. Title of project
2. Name of Team
3. Names and field of expertise of Team members
4. List of new pair-wise collaborations on Team (defined as individuals not having published together in the past 5 years)
5. Information about how Team learned about the Challenge
6. Identification of datasets used (1 page)
7. A description of methods used to generate the findings (4 pages maximum)

8. Narrative which addresses the evaluation criteria (identification of novel findings, replication of findings, innovation of approach, evidence of novel biological hypothesis(es), and collaboration) (6 pages maximum)
9. The corresponding source code so that the Challenge organizers can re-run and manually review and verify that the code affiliated with the top scoring Entries yield the submitted results.

Only complete Entries, which follow application instructions, will be reviewed and eligible to win. Top performing Entries will be reviewed thoroughly. The NCI reserves the right to disqualify any Challenge participants in instances where cheating or other misconduct is identified. Details regarding the dispute resolution process are provided on the Challenge website (<https://www.synapse.org/upforachallenge>).

Warranties

By submitting an Entry to the Challenge, Challenge participants represent and warrant that all information provided in their Entries and as a result of the Challenge registration process is true and complete, that Challenge participants have the right and authority to submit such Entry on their own behalf or on behalf of the persons and entities specified within the Entry, and that the Entry:

1. Is the Challenge participant's or Team's (as applicable) own original work, or is used by permission with full and proper credit given within the Entry;
2. Does not contain confidential information or trade secrets (the Team's or anyone else's);

3. Does not violate or infringe upon the patent rights, industrial design rights, copyrights, trademarks, rights of privacy, publicity or other intellectual property or other rights of any person or entity;
4. Does not contain malicious code, such as viruses, timebombs, cancelbots, worms, trojan horses or other potentially harmful programs or other material or information;
5. Does not and will not violate any applicable law, statute, ordinance, rule or regulation; and
6. Does not trigger any reporting or royalty obligation to any third party.

Amount of the Prize

The grand prize Entry will be awarded up to \$30,000. The second place Entry will be awarded a runner-up prize of up to \$20,000. Prizes will be awarded by Sage Bionetworks. The top 5 Entries (grand prize, second place, and the next three runner-ups) as well as the People's Choice Award winner will be highlighted on the Challenge and DCCPS EGRP websites pending selection by the NCI Director. The top 5 Entries (grand prize, second place, and the next three runner-ups) as well as the People's Choice Award winner will be invited to prepare a manuscript for publication describing their approach and results with a goal of a special journal issue highlighting the Challenge. All Challenge participants will be acknowledged in the special issue of the journal, pending acceptance.

The NIH reserves the right to cancel, suspend, and/or modify this Challenge at any time through amendment to this Federal Register notice. In addition, in the event the Challenge is modified, Challenge participants registered in the Challenge will be notified by email and provided with a copy of the amended Challenge rules and a listing of the changes

that were made. Any participant who continues to participate in the Challenge following receipt of such a notice of amendment, will be deemed to have accepted any such amendment. If a participant does not wish to continue to participate in the Challenge pursuant to the Official Rules, as amended, such participant may terminate his/her/ participation in the Challenge by not submitting additional Entries. The NIH reserves the right to not award any prizes if no Entries are deemed worthy.

Basis upon Which Winner Will Be Selected

Entries will be scored by the Challenge Evaluation Panel using the criteria listed below. After the Challenge Evaluation Panel provides final scores, the highest scoring applications will be evaluated for reproducibility by Sage Bionetworks' data scientists. In order to qualify for a Challenge prize, it must be possible for Sage Bionetworks' data scientists to reproduce Entry results within 1 month. The NCI Judges will review scores and reproduction by Sage and make recommendations to the NCI Director. The NCI Director will make the final selection of Entries for award.

Scoring Criteria (100 points)

1. Identification of Novel Findings (25 points) – Using breast cancer GWAS data sets available in dbGaP and/or any other publicly available data sets, Challenge participants must identify new genes or combinations of genes, genetic variants, or sets of genomic features associated with breast cancer susceptibility.
 - a. The [National Human Genome Research Institute's \(NHGRI\) Catalog of Published Genome Wide Association Studies](#) (<http://www.genome.gov/gwastudies/>) or variants/loci identified in the following publications can be used to evaluate possible novel findings:

- i. Mavaddat et al., 2010,
<http://www.ncbi.nlm.nih.gov/pubmed/?term=20542480>;
- ii. Ghoussani et al., 2013,
<http://www.ncbi.nlm.nih.gov/pubmed/?term=23973388>;
- iii. Fachal and Dunning, 2015,
<http://www.ncbi.nlm.nih.gov/pubmed/?term=25727315>

b. The scale for novelty for the Challenge Evaluation panel to use as a guide is provided:

- i. New variants in well-established high or moderate penetrance genes (e.g., BRCA1/BRCA2; ATM; PALB2) (low)
- ii. New variants in GWAS-identified genes or loci (med)
- iii. New combinations of variants which were previously identified (i.e., the combination or combined effect is new, but the variants were previously identified) (medium)
- iv. New genes or loci (high)
- v. New combinations of variants from genes or loci not identified previously (i.e., the combination and some of the variants are new) (high)

2. Replication of Findings (25 points) – Evidence of the validity of the proposed novel finding will be evaluated through replication.

- a. There are several different ways replication can be accomplished. These may include using data sets as testing and training data (or discovery in one data set and replication in another data set) or dividing the data into

several portions and performing some type of cross-validation. The Challenge Evaluation panel will also be open to other innovative approaches for replication.

- i. The Challenge participant will need to select criteria for replication and provide a justification for the selected criteria. Using the criteria selected by the Challenge participant, the Challenge participant must demonstrate replication of findings.
 - b. NOTE: Challenge participants should provide their criteria for replication in the narrative portion of their Challenge Entry.
 - c. The adequacy of criteria selected by the Challenge participant and evidence for replication will be scored by the Challenge Evaluation Panel.
3. Innovation of Approach (25 points) – Innovation and creativity of the submitted approach will be evaluated. Innovation will be defined as a new or significantly improved method. The submitted narrative must describe what is innovative about the approach, what this approach is building on, and why the approach is necessary or how it improves upon existing approaches. Some criteria for innovation include the following:
 - a. Does the Entry seek to shift current paradigms by utilizing novel theoretical concepts, approaches, or methodologies?
 - b. Are the concepts, approaches, or methods in the Entry novel to this field of research or novel in a broader sense?
 - c. Does the Entry represent a refinement, improvement, or new application of theoretical concepts, approaches, or methodologies?

4. Evidence of Novel Biological Hypothesis(es) (10 points) –

- a. Evaluation of this aspect of Challenge Entries will be based on whether findings (i.e., new genes or combinations of genes, genetic variants, or sets of genomic features) lead to novel biological hypotheses. A description of these hypotheses should be provided in the final project Entry.
- b. Novel biological hypotheses should be testable, either using computational or laboratory approaches. Evaluation will be based on the narrative description of the design of testable experiments, which could examine the novel biological hypothesis identified through these new genes or combinations of genes, genetic variants, or sets of genomic features associated with breast cancer. The format should mirror an outline of grant-specific aims.

NOTE: The “Evidence of Novel Biological Hypothesis(es)” criteria (4) is distinct from the “Identification of Novel Findings” criteria (1). The “Evidence of Novel Biological Hypothesis(es)” criteria (4) is based on the narrative description of hypotheses generated from the findings and proposed follow up experiments. In contrast, the “Identification of Novel Findings” criteria (1) are the identification of new genes or combinations of genes, genetic variants, or sets of genomic features associated with breast cancer susceptibility.

5. Collaboration (15 points) – Points will be awarded based on (a) the number of different fields represented on the Team; (b) the number of new collaborations represented on the Team (defined as individuals not having published together in the past 5 years); and (c) the number of individuals invited to participate in the Challenge by Team members resulting in Entries to the Challenge.

People's Choice Award

In addition to the main prize, a People's Choice Award for the most interesting strategy may be given to the Entry that receives the most votes from the Challenge participants on the Challenge website. Details of how voting will take place will be posted on the Challenge website.

Additional Information

Intellectual Property

By submitting an Entry, each Challenge participant warrants that he or she is the sole author and owner of any copyrightable works that the Entry comprises, that the works are wholly original with the Challenge participant (or is an improved version of an existing work that the Challenge participant has sufficient rights to use and improve), and that the Entry does not infringe any copyright or any other rights of any third party of which Challenge participant is aware.

To receive an award, Challenge participants will not be required to transfer their exclusive intellectual property rights to the NIH. Each individual (whether competing singly or on a team) or entity retains title and full ownership in and to their Entry and expressly reserves all intellectual property rights (e.g., copyright) in their Entry.

However, by participating in the Challenge each individual (whether competing singly or in a team) grants to the NCI and others acting on behalf of the NCI, a royalty-free non-exclusive worldwide license to use, copy for use, and display publicly all parts of the Entry for the purposes of the Challenge. This license may include posting or linking to the Entry on the official NCI Challenge website and making it available for research use by the public.

When submitting source code as part of the Entry package, participants should provide it to the NCI under an open-source license of their choice. The license must permit the NCI contractor, Sage Bionetworks, to distribute the code to the public for non-commercial research and development use via the Synapse challenge platform. Participants may keep copyright to their code Entries. If participants do not provide information on licensing, participant's Entry shall be under the FreeBSD license.

Challenge participants are free to discuss their Entry and the ideas or technologies that it contains with other parties and are free to contract with any third parties as long as they do not sign any agreement or undertake any obligation that conflicts with any agreement that they have entered into (i.e., with Team members) or do enter into regarding their Entry for the Challenge. For the purpose of clarity, Challenge participants acknowledge that the intent of the Challenge is to encourage people to collaborate and share ideas and innovations.

By submitting an Entry, Challenge participants grant the NCI and the contractor Sage Bionetworks the limited rights set forth in these Official Rules. By submitting an Entry, each participant (whether competing singly or on a team) grants to the NCI and Sage Bionetworks the right to review their Entry and to have the NCI and their designees review the Entry.

Liability and Indemnification

By participating in this Challenge, each Challenge participant (whether competing singly or on a Team) agrees to assume any and all risks and waive claims against the Federal government and its related entities, including Sage Bionetworks, the Challenge Evaluation Panel and the NCI Judges, except in the case of willful misconduct, for any

injury, death, damage, or loss of property, revenue, or profits, whether direct, indirect, or consequential, arising from participation in this Challenge, whether the injury, death, damage, or loss arises through negligence or otherwise. By participating in this Challenge, each Challenge participant (whether competing singly or on a team) agrees to indemnify the Federal government and the contractor Sage Bionetworks, against third party claims for damages arising from or related to Challenge activities.

Insurance

Based on the subject matter of the Challenge, the type of work that it will possibly require, as well as an analysis of the likelihood of any claims for death, bodily injury, or property damage, or loss potentially resulting from competition participation, Challenge participants are not required to obtain liability insurance or demonstrate financial responsibility in order to participate in this Challenge.

Challenge Judges

Huann-Sheng Chen; Mathematical Statistician; Statistical Methodology and Applications Branch (SMAB); Surveillance Research Program (SRP); DCCPS; NCI

Eric J. Feuer; Ph.D.; Chief, SMAB; SRP; DCCPS; NCI

Leah Mechanic; Ph.D.; Program Director; Genomic Epidemiology Branch (GEB); Epidemiology and Genomics Research Program (EGRP); DCCPS; NCI

Elizabeth Gillanders; Ph.D.; Chief; GEB; EGRP; DCCPS; NCI

Carolyn M. Hutter, Ph.D.; Program Director; Division of Genomic Medicine; National Human Genome Research Institute

Margaret A. Tucker, M.D., Director, Human Genetics Program and Acting Chief, Laboratory of Translational Genomics; Division of Cancer Epidemiology and Genetics; NCI

Date: May 19, 2015

Douglas R. Lowy, M.D.

Acting Director, National Cancer Institute

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